



IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicant(s): Hiroyuki MIYATA et al.

Serial No. : 09/988,042

Filed : November 16, 2001

For : 7a-ALKOXY-4H-PYRANO[3,2-d]-OXAZOL-2(3H)-ONE
AND PROCESS FOR PRODUCING THE SAME

Art Unit : 1626

Examiner : Rebecca L. Anderson

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

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DECLARATION UNDER 37 CFR 1.132

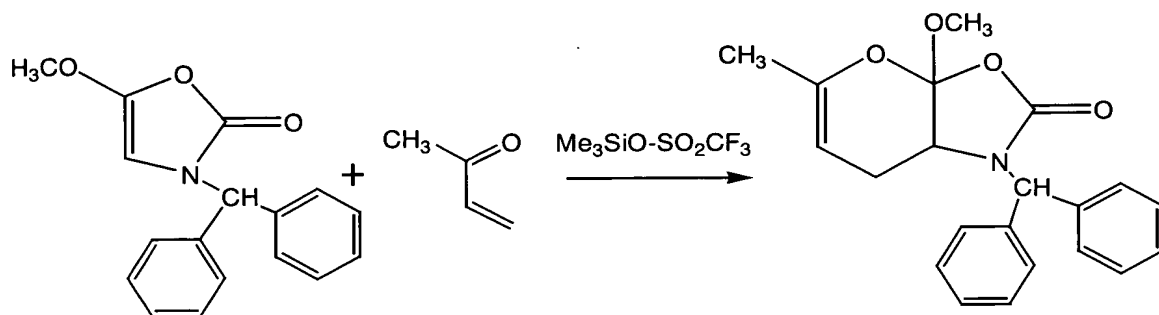
S I R :

I. I, Hiroyuki MIYATA, a citizen of Japan, who declares and says that:

I am an inventor of the present U.S. Patent Application as identified above and understand the English language. I studied the Official Action dated April 30, 2002 received in said application, and in order to prove the utility of the compounds claimed in the present application, the following experiments were carried out under my supervision.

II. Experiments

Example 1: Synthesis of 3-diphenylmethyl-7a-methoxy-6-methyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one (R¹=1-diphenylmethyl group, R²=hydrogen atom, R³=methyl group and R⁴=methyl group)



To a 50 ml glass flask equipped with a stirrer, a thermometer and a dropping funnel were added 140.7 mg (0.50 mmol) of 3-diphenylmethyl-5-methoxy-2(3H)-oxazolone and 3.0 ml of methylene chloride and the mixture was cooled down to -78°C under nitrogen atmosphere. Subsequently, 52.6 mg (0.75 mmol) of methyl vinyl ketone and 9.1 μl (0.05 mmol) of trimethylsilyltriflate were added thereto and a reaction was carried out for 2 hours at the same temperature. After completion of the reaction, 15 ml of an aqueous solution of saturated sodium hydrogen carbonate was added thereto and the mixture was extracted with 15 ml of methylene chloride. After separating the organic layer (methylene chloride layer), it was washed twice with each 15 ml of water, and then, it was dried over anhydrous magnesium sulfate. It was then subjected to filtration and the resultant filtrate was concentrated under reduced pressure to give 200 mg of an oily product. This was purified by a silica gel column chromatography (eluent: n-hexane/ethyl acetate = 20/1 (volume ratio)), to obtain 158.4 mg of 3-diphenylmethyl-7a-methoxy-6-methyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one as white crystal (isolation yield: 90%; based on 3-diphenylmethyl-5-methoxy-2(3H)-oxazolone).

The 3-diphenylmethyl-7a-methoxy-6-methyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one is a novel compound having physical properties shown below.

$^1\text{H-NMR}$ (δ (ppm), CDCl_3): 1.80 (m, 2H), 1.86 (s, 3H), 3.59 (s, 3H), 3.73-3.75 (m, 1H), 4.81-4.84 (m, 1H), 6.27 (s, 1H), 7.25-7.40 (m, 10H)

$^{13}\text{C-NMR}$ (δ (ppm), CDCl_3): 19.1, 23.5, 50.5, 51.1, 59.8, 99.9,

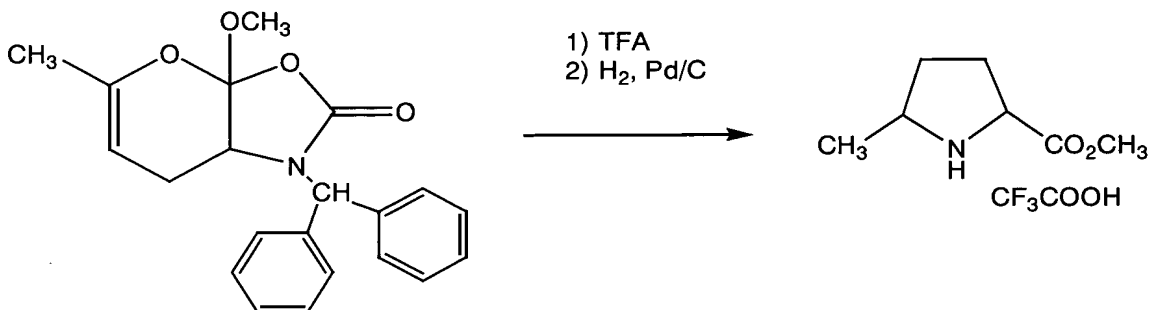
115.9, 127.8, 128.1, 128.2, 128.5, 128.7, 128.8, 137.6, 138.6,
150.8, 155.2

MS (CI, $i\text{-C}_4\text{H}_{10}$) m/z : 352 (MH^+)

Elemental analysis(%): Calcd.: C;72.58, H;5.37, N:4.98,

Found: C;72.45, H;5.40, N:4.98.

Reference Example 1 (synthesis of trifluoroacetate of 5-methylproline methyl ester)



To a 50 ml glass flask equipped with a stirrer, a thermometer and a dropping funnel were added 932.6 mg (2.65 mmol) of 3-diphenylmethyl-7a-methoxy-6-methyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one synthesized in the same manner as in Example 1, 906.5 mg (7.95 mmol) of trifluoro acetate and 26 ml of methylene chloride, and the mixture was reacted under argon atmosphere at room temperature for 17 hours. Subsequently, 26 ml of methanol and 564 mg of 5% by weight Pd/C were added thereto and reaction was carried out under hydrogen gas atmosphere (under normal pressure) at room temperature for 16 hours. After completion of the reaction, the reaction mixture was filtrated and the resultant filtrate was concentrated under reduced pressure to give 1228 mg of colorless transparent oily product. This was washed with each 20 ml of diethyl ether for 3 times, with each 20 ml of n-hexane for 2 times and with 20 ml of diethyl ether for once in this order, and dried under reduced pressure to give 534 mg of trifluoroacetate of 5-methylproline methyl ester as white crystal (isolation yield: 78%; based on 3-diphenylmethyl-7a-methoxy-6-methyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one).

Physical properties of the trifluoroacetate of 5-methylproline methyl ester are shown below.

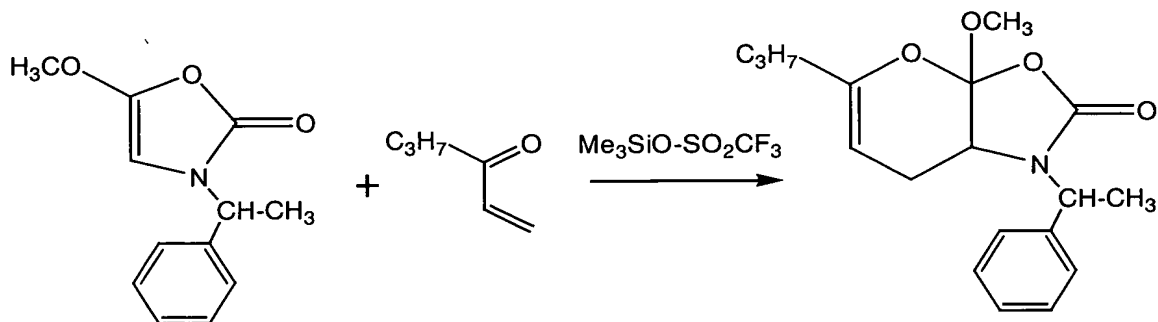
$^1\text{H-NMR}$ (δ (ppm), CDCl_3): 1.51 (d, $J=6.4\text{Hz}$, 3H), 1.61-1.72 (m, 1H), 2.19-2.32 (m, 2H), 2.40-2.52 (m, 1H), 3.85 (s, 3H), 3.85-3.94 (m, 1H), 4.53 (dd, $J=9.3\text{Hz}$, $J=4.9\text{Hz}$, 1H),
 $^{13}\text{C-NMR}$ (δ (ppm), CDCl_3): 17.7, 28.4, 31.4, 53.7, 56.8, 59.0, 170.3

MS (CI, $i\text{-C}_4\text{H}_{10}$) m/z : 144 (MH^+), 84

Elemental analysis(%): Calcd: C;42.03, H;5.49, N:5.42,

Found: C;41.74, H;5.48, N:5.44.

Additional Example: Synthesis of 3-(R)-1-phenylethyl-7a-methoxy-6-propyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one ($\text{R}^1=1\text{-phenylethyl}$ group, $\text{R}^2=\text{hydrogen}$ atom, $\text{R}^3=\text{methyl}$ group and $\text{R}^4=\text{propyl}$ group)



In 25 ml of methylene chloride was dissolved 1.096 g (5.0 mmol) of 3-(R)-1-phenylethyl-5-methoxy-2(3H)-oxazolone and the mixture was cooled to -78°C . To the solution were added 736 mg (7.5 mmol) of 1-hexen-3-one and 90 μl (0.5 mmol) of trimethylsilyl trifluoromethanesulfonate, and the resulting mixture was stirred at the same temperature for 2 hours. To the mixture was added 25 ml of an aqueous saturated sodium hydrogen carbonate solution and the reaction mixture was extracted with 25 ml of methylene chloride. The methylene chloride layer was washed twice with each 20 ml of water, dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated under reduced pressure to obtain 1.80 g of an oily product. The resulting oily product was purified by silica gel

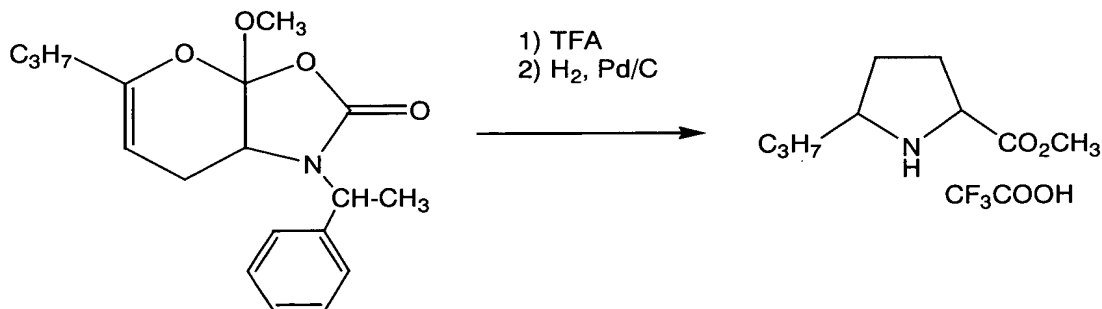
column chromatography (eluent; n-hexane:ethyl acetate=9:1 (volume ratio)) to obtain 1.02 g (3.21 mmol) of a diastereomer mixture of 3-(R)-1-phenylethyl-7a-methoxy-6-propyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one as a colorless transparent oily product (Yield of the resulting compound based on 3-(R)-1-phenylethyl-5-methoxy-2(3H)-oxazolone = 64%). A formation ratio of the diastereomers was 70 : 30 by the analysis of HPLC. Spectrum data of the diastereomer mixture are shown below.

•MS (CI, i-C₄H₁₀) m/z: 318 (MH⁺), 105

•¹H-NMR (δ ppm, CDCl₃) major isomer: 0.89-0.96 (t, J=7.8Hz, 3H), 1.47-2.20 (m, 6H), 3.60 (s, 3H), 3.95 (dd, J=2.9Hz, J=5.4Hz, 1H), 4.48 (dd, J=3.4Hz, J=6.3Hz, 1H), 5.19 (q, J=7.3Hz, 1H), 7.25-7.42 (m, 5H).

minor isomer: 0.89-0.96 (t, J=7.8Hz, 3H), 1.47-2.20 (m, 6H), 3.55 (s, 3H), 3.58 (t, J=4.9Hz, 1H), 4.47 (t, J=4.9Hz, 1H), 5.10 (q, J=7.3Hz, 1H), 7.25-7.42 (m, 5H).

Additional Reference example: Introduction of 5-(n-propyl)-proline methyl ester to trifluoroacetate



In 20 ml of methylene chloride was dissolved the diastereomer mixture of 3-(R)-1-phenylethyl-7a-methoxy-6-propyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one (634 mg, 2.0 mmol) obtained in Additional Example 1, and to the solution was added trifluoroacetic acid (684 mg, 6.0 mmol) under argon gas atmosphere and the mixture was reacted at room temperature for 18 hours. Next, methylene chloride was removed under reduced pressure, and 15 ml of methanol and 500 mg of 5% Pd/carbon were added to the concentrated residue. The resulting mixture was reacted under hydrogen gas atmosphere (1 atm) at room temperature for 20 hours. The reaction mixture was filtered

and the filtrate was concentrated under reduced pressure to obtain 610 mg of a pale yellowish transparent oily substance. To the oily substance was added 10 ml of diethyl ether to crystallize the substance, and the resulting crystals were dried under reduced pressure to obtain 230 mg of 5-(n-propyl)-proline methyl ester trifluoroacetate as a white crystal. The resulting compound showed a single NMR chart so that it was confirmed to be a single isomer (Yield based on 3-(R)-1-phenylethyl-7a-methoxy-6-propyl-4H-pyrano[3,2-d]-oxazol-2(3H)-one = 40%).

•Melting point: 115-118°C

•MS (CI, i-C₄H₁₀) m/z: 172 (MH⁺), 112

•¹H-NMR (δ ppm, CDCl₃): 0.97 (t, J=7.3Hz, 3H), 1.37-1.52 (m, 2H), 1.62-1.75 (m, 2H), 1.85-1.97 (m, 1H), 2.15-2.31 (m, 2H), 2.36-2.49 (m, 2H), 3.67-3.77(m, 1H), 3.82 (s, 3H), 4.47-4.52 (m, 2H).

3. Conclusion

From the results of Additional Reference example, it would be clear that the intermediate compound of the present invention can be clearly led to a final product (proline).

Other compounds than the above claimed in the scope of the present invention can be also led to the final product in the same manner as mentioned above.

Thus, I believe that the compounds of the present invention can be easily led to the final product for those skilled in the art even when there is no specific disclosure about the synthetic method of the final product other than Reference Example 1 mentioned on pages 41-42 of the present specification.

IV. I further declare that all statements made herein of my own knowledge are true and that all statements made in information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or

imprisonment, or both, under Section 1001, of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 10/23/2002 Hiroiyuki Miyata
Hiroiyuki MIYATA